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REPLY

We read with interest the letter of Schnyder and Turi, and are not surprised that our study reporting increased complications associated with arteriotomy closure devices (ACD) has engendered such a strong and obviously heartfelt response. When a negative study is generated and subsequently published in the pursuit of academic honesty and patient well-being (our overriding motivation), one must regretfully anticipate one-sided and dogmatic reactions from parties who, in the name of honesty and patient well-being, have the recollection or documentation.

Schnyder and Turi are correct though in pointing out potential hidden physician prejudices; the operators in the present study were “biased” to tend to use these devices in ideal patients, explaining why procedure duration was less in patients receiving ACDs, and in whom less debulking and more stand-alone angioplasty were performed, requiring smaller sheaths (2). Nonetheless, complications were still increased with closure devices despite these predispositions favoring the ACD group. We further acknowledge that the increased activated clotting time (ACT) levels at the time of closure device insertion likely favored more bleeding in the ACD group (1). However, the ability to withdraw sheaths in the catheter laboratory in the fully anticoagulated patient, rather than waiting 4 to 6 h for sheath extraction in the in-patient telemetry unit prior to manual compression, is a purported advantage of ACDs and the standard way these devices are utilized. Certainly, Schnyder and Turi are not suggesting ACT normalization is required before using a closure device, which would obviate much of the device’s clinical desirability.

Schnyder and Turi criticize the physicians involved in this study as being “largely novices at vascular closure, having apparently failed to adopt them in routine use.” The great majority of the closure procedures were performed by four senior physicians, who collectively have performed >25,000 PCI procedures and many more diagnostic angiograms. They note, however, that only ~150 ACD procedures were being done per year in the study by these physicians; this is true if only “interventional” procedures are considered—the same four operators performed approximately two- to threefold this many closure procedures annually on diagnostic patients. Furthermore, the physicians involved have been participating investigators in most of the premarket approval ACD clinical trials. Thus, while we do not profess to possess the expertise of Schnyder and Turi, the volume and experience with ACDs represented in the present report certainly would more than match the real-world qualifications of most centers experienced in both traditional and novel methods of arteriotomy closure.

Schnyder and Turi also repeatedly note that not all patients in our study had a preclosure femoral angiogram. Though we did not collect this data, we believe >90% of patients did undergo such examination, a frequency that is likely greater than at most hospitals using ACDs in the “real world.” Indeed, one reason why more patients did not receive closure devices in our study was the low threshold in place to exclude patients upon the identification of disease or calcification at the access site, an excessively low puncture, or small vessel diameter. Furthermore, femoral angiography was not performed in the manual compression group, and cases unsuitable for closure devices on the basis of the angiogram were also included in the manual compression group, both factors that would favor the ACD group. Finally, to our knowledge, no prior study (whether real-world or controlled trial) has ever reported the actual frequency with which the recommended femoral angiogram was in fact performed.

Schnyder and Turi state that “multiple studies have reported far larger experiences” (2–4), taking issue with our statement that large postapproval studies with these devices were lacking. At the time of submission for publication, our analysis of 6,408 interventional procedures was indeed the only large experience with >500 ACDs investigating femoral access complications after PCI; the three referenced single-center studies were published afterward. Regardless, these subsequent experiences largely support our findings.
In the observational study by Cura et al. (2) comparing the outcomes of manual compression with ACDs in 2,918 patients, the suture-based device was associated with increased rates of vascular access site infections (0.5% vs. 0%) and need for surgery (1.0% vs. 0.4%) compared with manual compression, while both suture and collagen plug ACDs resulted in increased rates of retroperitoneal hematoma (despite the institutional requirement for femoral angiograms before device usage), and a trend toward doubling of the rate of access site–related blood transfusions. In the 3,699-patient quality control study of Carey et al. (3), compared with manual compression the collagen plug devices resulted in greater rates of major vascular complications and hospital readmission, whereas both collagen plug and suture-based ACDs increased rates of infection.

Finally, Schnyder and Turi reference the 930-patient study of Balzer et al. (4), in which a suture-based closure device was used in all patients, with no control group. Technical success was achieved in only 92% of patients, and a relatively high rate of patients (7.0%) had an access site complication, including a 4.1% incidence of large hematomas (>6 cm). They described a learning curve for technical success extending beyond 350 treated patients (although it is unclear how many operators performed these procedures, and whether or not the rate of complications decreased with experience). In any event, one can question the wisdom of using a costly device to replace something as simple and effective as manual compression if >350 procedures are required for mastery!

Thus, the bulk of data (not rhetoric) generated to date supports the contention that vascular closure devices may increase complications in patients undergoing percutaneous interventional procedures. Certainly, no studies exist to suggest that complications are decreased with these devices. Given the fact that ACDs are used primarily for patient comfort (or more rapid ambulation, although the potential economic gains from early discharge in this regard have not been realized owing to insurance requirements of an overnight stay after PCI for full reimbursement), and add significant capital cost to an already extended healthcare budget, we question whether closure devices should be used in post-PCI patients prior to demonstration of their safety in an adequately powered postmarket registry study. In this regard we are concerned that Schnyder and Turi, based on no firm academic footing, “use these devices after percutaneous intervention in nearly 100% of . . . cases” and feel that further recommendations “should await the results of prospective, randomized studies.” While the call for randomized controlled studies can never be criticized, Schnyder and Turi are no doubt aware that such a trial, designed to show noninferiority in vascular complications between manual compression and ACDs with a relative delta of 20%, would require enrollment of >8,000 patients, and will thus never be performed. Moreover, though this is not the first time the researchers have been critical of other investigators’ work in this field (5), to our knowledge they have not reported their own patient outcomes with and without closure devices, which would be welcome.

In the final analysis, in the interest of our patients we must not succumb to the hazards of anecdotal medicine or the lure of the latest and greatest drug or device. For this reason the results of all credible large-scale postmarket studies, whether prospective, retrospective, case-controlled or registry-based, must be seriously considered by the thoughtful operator in light of the physician’s Hippocratic oath—primum non nocere—first, do no harm. A few additional hours of patient comfort or nursing convenience does not justify even a 1% increase in the rate of septic endarteritis, large hematoma, or the need for blood transfusion or vascular surgical repair. Even the Food and Drug Administration, the unconditional guardian of the public health, realizes the limitations inherent in the best intentioned premarket studies, and thus the need for vigorous postmarket surveillance (6). We remain hopeful that with increasing operator experience and technical device evolution the promise of ACDs will be realized, and we implore the collaboration of our physician–scientist, regulatory and industry partners to obtain confirmatory evidence.

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Dobutamine Stress Testing Revisited

I read with great interest the recently published study by Calnon et al. (1), which analyzed the clinical outcome of patients who underwent dobutamine stress single-photon emission computed tomography (SPECT) Tc-99m-sestamibi imaging. Two aspects of this study are rather intriguing, and deserve further examination.

First, the annual “hard” cardiac event rate in patients with normal dobutamine SPECT studies was 2.3%. This is more than twofold higher than previously published event rates after a normal exercise stress perfusion study (<1%). It is also substantially higher than previously reported in other patients with normal dobutamine SPECT. Previous studies, including a large series by Geleijnse et al. (2), reported an annual event rate of 0.8% for hard events, and 2.5% for all cardiac events in patients with normal dobutamine Tc-99m-sestamibi SPECT studies. As stated by the investigators (1), some “probably normal” studies were grouped into the “normal study” category, and neither attenuation correction nor gated analyses were used in most studies. It is possible that these factors may have affected observed event rates.

Second, the multivariate analysis identified the electrocardiogram (ECG) response and SPECT perfusion results as independent predictors of cardiac events after accounting for clinical variables. As a group, patients with abnormal ST-segment changes and normal myocardial perfusion had a similar intermediate rate of events as did those with perfusion defects but without abnormal ST-segment changes on their ECG. This is a very interesting finding, and has the potential for changing our common clinical practice.

It may be helpful to separate the two groups with intermediate event rates and report the outcome separately for each group. Commonly, patients with SPECT scans revealing no perfusion abnormalities or ancillary findings suggestive of coronary artery disease, but with ischemic ST-segment changes during dobutamine stress, are often classified as “normal.” Thus, it will be particularly useful to know whether the outcome in this group differed significantly from a subgroup of dobutamine stress patients with normal ECG and normal perfusion. If, indeed, patients with normal ST-segment changes but normal perfusion during dobutamine stress testing have an intermediate event rate, it would be interesting to know whether any significant clinical variables might explain a relatively high event rate in this subset.

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REPLY

Our observation of a relatively high cardiac event rate in patients with normal dobutamine Tc-99m-sestamibi single-photon emission computed tomography (SPECT) studies must be considered in the context of the high intrinsic risk of the population referred for dobutamine perfusion imaging at our institution (1). We reserve dobutamine for patients who are unable to perform adequate exercise and have contraindications to adenosine or dipyridamole stress. Geleijnse et al. (2) used dobutamine more liberally (e.g., included patients without contraindications to vasodilator stress), which might have contributed to the lower cardiac event rates observed in patients with normal dobutamine Tc-99m-sestamibi SPECT studies at their institution. Geleijnse et al. (2) assigned patients with “equivocal defects” to the “normal scan” group, and studies were interpreted without the use of electrocardiogram (ECG)-gating or attenuation correction. It is therefore unlikely that these technical factors were responsible for the higher cardiac event rates in patients with normal dobutamine Tc-99m-sestamibi SPECT scans in our study. We believe that the higher cardiac event rates reflect the high intrinsic risk of the population referred for dobutamine perfusion imaging at our institution. This conclusion is supported by the significantly higher cardiac event rate in patients with abnormal dobutamine Tc-99m-sestamibi SPECT studies (1) than in patients with abnormal exercise Tc-99m-sestamibi SPECT studies (3).

We agree that the subgroup of patients (n = 23) with dobutamine-induced ST-depression and normal SPECT results is of particular clinical interest. Absence of a perfusion defect could have resulted from “balanced” myocardial ischemia due to diffuse coronary disease without a normally perfused myocardial region, though this phenomenon is rare and unlikely to have occurred in all 23 patients. Only three total cardiac events were observed in this subgroup (one cardiac death and two nonfatal myocardial infarctions [MIs]), but the annual cardiac event rates were relatively high owing to the small sample size (cardiac death and nonfatal MI rates of 2.6% and 5.2%, respectively). These findings should be confirmed in a larger group of patients before specific recommendations are made regarding management of patients with dobutamine-induced ST-depression and normal SPECT images.

The larger subgroup of patients (n = 129) with normal ECG responses but abnormal SPECT images had a high rate of cardiac events (10 cardiac deaths [4.5%/year] and 8 nonfatal MIs [3.6%/year]). This subgroup of patients should be considered at high risk for cardiac events and should be managed accordingly.

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